REMARKS

Applicants respectfully request reconsideration of this application.

I. Summary of the Claimed Invention

The claimed invention is directed to the surprising discovery of controlled release nanoparticulate active agent compositions, methods of preparing such compositions, and methods of treating mammals using such compositions.

The controlled release compositions provide for the therapeutically effective release of an incorporated nanoparticulate active agent in a patient for a time period ranging from about 2 to about 24 hours. This discovery was surprising because nanoparticulate active agent compositions are designed for immediate, fast release. Such fast release results from the nanoparticulate size of the active agent, having a large surface area in relation to the volume, which results in rapid dissolution of the active agent following administration. However, rapid dissolution is contrary to the goal of controlled release formulations.

Applicants unexpectedly discovered that nanoparticulate active agent compositions could be effectively formulated into controlled release compositions. This is not shown or suggested by the cited prior art.

II. The Claimed Invention is Patentable Over Liversidge

Claims 1-22 and 25-53 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,145,684 ("Liversidge"). Applicants respectfully traverse this ground for rejection.

A. Summary of Liversidge

The claimed invention constitutes an improvement over commonly-owned Liversidge. *See* page 5, lines 25-27, of the application. Liversidge teaches compositions comprising nanoparticulate active agents and surface stabilizers, but the reference does not teach or suggest incorporation of such nanoparticulate active agent compositions into controlled release dosage forms.

B. The Mere Presence of One or More Cellulosic Polymers Does Not Provide Controlled Release of a Nanoparticulate Active Agent Composition

In support of the rejection, the Examiner stated that:

> the teaching of cellulose polymers in the composition [of Liversidge] reads on applicant's claim to both a surface stabilizer and a rate controlling polymer, because on page 12, lines 27-28, applicant states that a suitable surface stabilizer includes various polymers, therefore the cellulose polymers can perform both desired functions.

Office Action at page 3.

The mere presence of a cellulosic polymer will not provide controlled release of a nanoparticulate active agent composition. Rather, as specified in the claimed invention, the structure of the composition, in combination with the presence of a rate controlling polymer, such as a cellulosic polymer, provides for controlled release of the nanoparticulate active agent.

Specifically, the claimed invention provides that the nanoparticulate active agent composition is either integrated in a rate-controlling matrix with the rate-controlling polymer, or the nanoparticulate active agent composition is coated with the rate-controlling polymer, such that the controlled release composition provides controlled release of the nanoparticulate active agent for a time period ranging from about 2 to about 24 hours.

Applicants have provided numerous working examples exemplifying the controlled release nanoparticulate active agent compositions of the invention, which are summarized in a chart attached as Exhibit 1. Column 1 of the chart provides the example number; if more than one solid dose formulation was made in the example, the formulations are identified as "a", "b", *etc.* Column 2 of the chart identifies the location of the example in the specification and the relevant figure, if appropriate. Column 3 identifies the active agent present in the solid dose (naproxen, glipizide, or nifedipine), and column 4 identifies the surface stabilizer(s) utilized in the nanoparticulate active agent composition. Column 5 identifies the components of the spray dried intermediate (SDI) or spray granulated intermediate (SGI), and the quantity of SDI or SGI, used to make the solid dosage form. As described in more detail in the examples, in making the controlled release nanoparticulate active agent dosage forms, a nanoparticulate active agent dispersion was first formulated into an SGI or SDI. The SGI or SDI was then subsequently combined with at least one rate controlling polymer and

excipients to make a controlled release composition. Column 6 identifies the rate controlling polymer and excipients present in the solid dosage form. Finally, column 7 provides the dissolution time in water of the solid dose controlled release nanoparticulate active agent composition.

The rate-controlling polymers used to make the controlled release compositions include, for example, hydroxypropylcellulose (HPC) and hydroxypropylmethylcellulose (HPMC) (now known as hypromellose). Controlled release of the nanoparticulate active agent compositions described in the examples of the application ranged from about to 2 to about 24 hours, which is consistent with Applicants' claimed invention.

The failure of compositions such as those described by Liversidge to deliver controlled release is exemplified by a comparison of the nanoparticulate active agent compositions of the invention, comprising cellulosic compounds and designed to exhibit controlled release, and nanoparticulate active agent compositions comprising cellulosic compounds and designed to exhibit immediate release. Such compositions are disclosed in co-owned U.S. Patent No. 6,316,029 for "Rapidly Disintegrating Oral Dosage Form" ("the '029 patent"), a copy of which is attached as Exhibit 2.

The examples of Liversidge do not utilize cellulosic polymers. Thus, Applicants' are submitting a summary of the relevant examples of the '029 patent to satisfy the Examiner's request for a submission of data showing immediate release nanoparticulate active agent compositions comprising a cellulosic polymer.

The data presented in Exhibit 1 is in sharp contrast to the data presented in a chart attached as Exhibit 3, which summarizes immediate release rates of compositions comprising nanoparticulate active agents and at least one cellulosic polymer. Exhibit 3 summarizes relevant examples from the '029 patent describing the dissolution of solid dose forms of a nanoparticulate active agent and a cellulosic surface stabilizer, such as hydroxypropyl cellulose (HPC). The active agents utilized in the examples include naproxen, glipizide, and nifedipine, which are also utilized in the examples of the invention. However, in contrast to the dissolution rate of about 2 to about 24 hours for the compositions of the invention, Exhibit 3 shows dissolution rates of ***33 seconds to 111 seconds***.

The data presented in Exhibits 1 and 3 demonstrates that the *structure* of a composition comprising a nanoparticulate active agent, in *combination* with a rate-controlling polymer, provides controlled release. The mere presence of a rate-controlling polymer in the

absence of such a structure will not provide controlled release of the nanoparticulate active agent. Thus, a polymer that is merely associated with the surface of an active agent to maintain a particle size (*i.e.*, functioning as a surface stabilizer), such as disclosed by Liversidge, will not have a rate-controlling effect.

As Liversidge does not teach or suggest Applicants' claimed invention, withdrawal of this ground for rejection is respectfully requested.

III. The Claimed Invention is Patentable Over Liversidge in View of Vernon or Chang

Claims 1, 10, and 54 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Liversidge in view of WO 95/22318 to Vernon ("Vernon") or U.S. Patent No. 5,188,755 to Chang et al. ("Chang"). Applicants respectfully traverse this ground for rejection.

Vernon and Chang are cited by the Examiner as teaching specific rate controlling polymers. This teaching does not overcome the deficiency of Liversidge, as given the teachings of Liversidge, Vernon, and Chang, one of skill in the art at the time the claimed invention was made would not have been motivated to combine the nanoparticulate active agent compositions of Liversidge with the rate controlling polymers of Vernon or Chang. Moreover, nor would one of skill in the art at the time the claimed invention was made have a reasonable expectation of success in obtaining the claimed invention, given the teachings of Liversidge and Vernon or Chang.

Liversidge teaches that small particle compositions are desirable because of their rapid dissolution:

> [i]t is known that the rate of dissolution of a particulate drug can increase with increasing surface area, i.e., decreasing particle size. . . . This invention is based partly on the discovery that drug particles having an extremely small effective average particle size can be prepared . . ., [which] can [then] be formulated into pharmaceutical compositions exhibiting unexpectedly high bioavailability.

Thus, one of skill in the art at the time the claimed invention was made would associate Liversidge with fast onset pharmaceutical compositions, because of the rapid dissolution of the nanoparticulate active agent compositions, and not with controlled release compositions.

Accordingly, there is no motivation to combine the teaching of Liversidge with the rate controlling polymers of Vernon or Chang.

Moreover, one of skill in the art at the time the claimed invention was made would not have had a reasonable expectation of success in being able to formulate the nanoparticulate active agent compositions of Liversidge into a controlled release composition. This is because first, Liversidge teaches that nanoparticulate active agent compositions have a very fast dissolution rate. Second, at the time the claimed invention was made, prior art references taught that designing controlled release compositions was difficult: "[d]esign of a sustained-release product is normally a very difficult task . . ." *See* Chang et al., "Sustained Drug Release from Tablets and Particles through Coating," Lieberman et al., eds., *Pharmaceutical Dosage Forms: Tablets*, Vol. 3, p. 201 (Marcel Dekker, Inc., New York) (already of record).

Accordingly, as one of skill in the art at the time the claimed invention was made would not have been motivated to combine Liversidge with Vernon or Chang, and as one of skill in the art at the time the claimed invention was made would not have had a reasonable expectation of success in being able to formulate the nanoparticulate active agent compositions of Liversidge into a controlled release composition, given the teachings of Vernon or Chang, withdrawal of this ground for rejection is respectfully requested.

IV. Conclusion

Applicants courteously request reconsideration of this application in view of the above remarks. This application is now in condition for allowance, and early notice to that effect is respectfully solicited.

If any fees are due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 that is not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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